Ospedale San Paolo
Polo Universitario

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

UNIVERSITÀ DEGLI STUDI DI MILANO

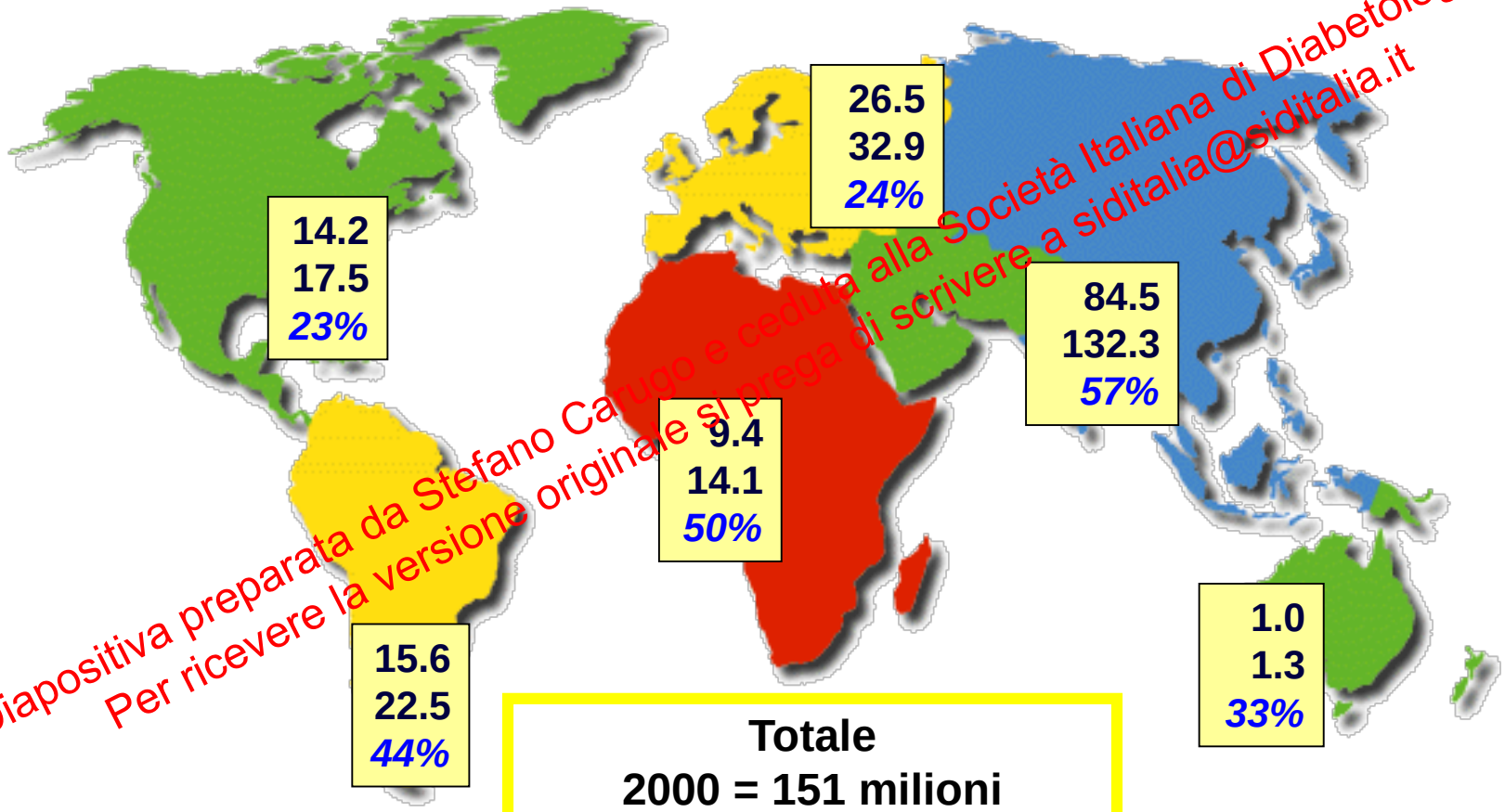
Il cuore del paziente diabetico

Milano 7 Luglio 2017

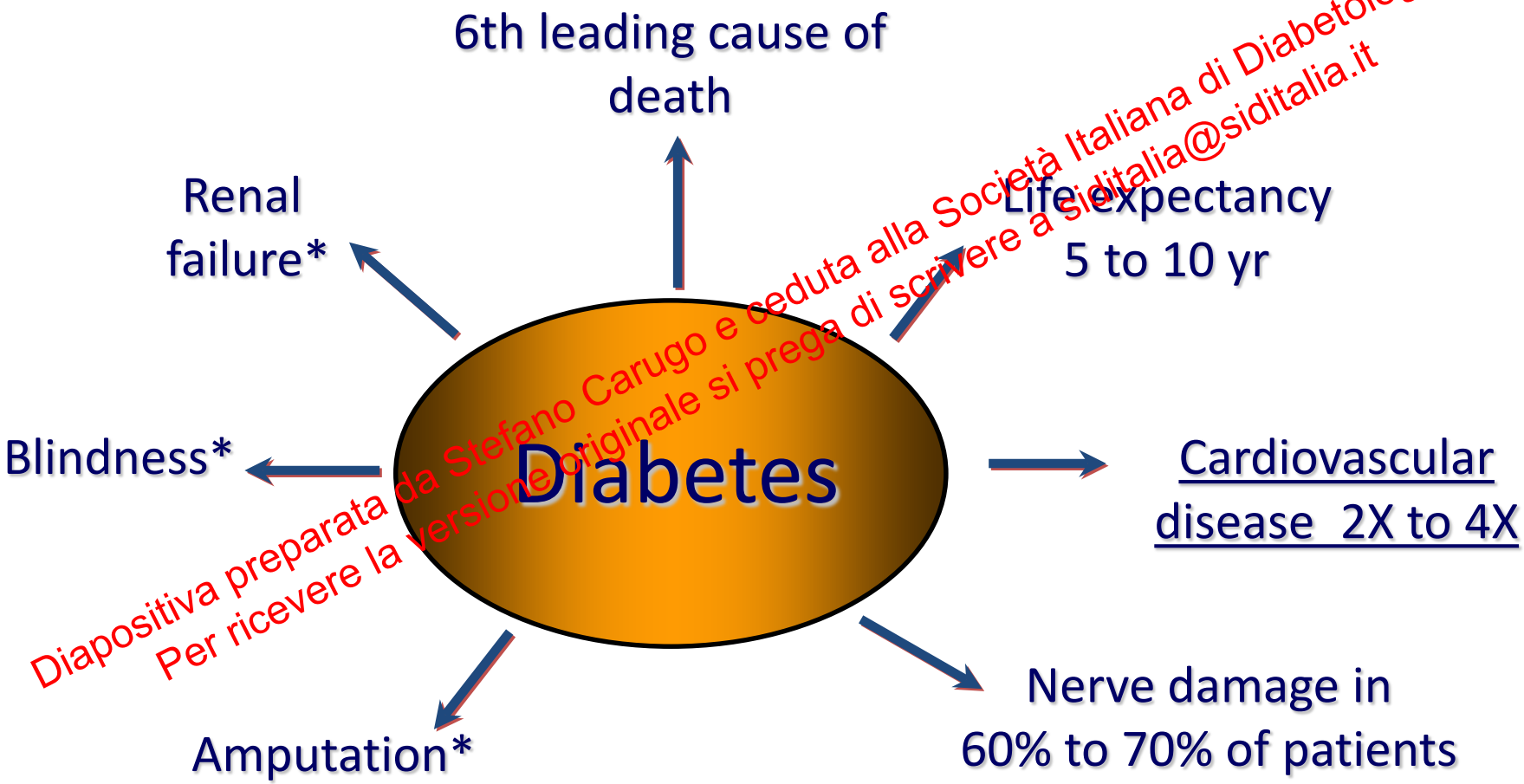
Prof. Stefano Carugo

Centro Cuore San Paolo

Proiezioni globali per l'epidemia di diabete : 2000–2025



Diabetes Mellitus: Health Impact of the Disease



*Diabetes is the no. 1 cause of renal failure, new cases of blindness, and nontraumatic amputations

Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus.

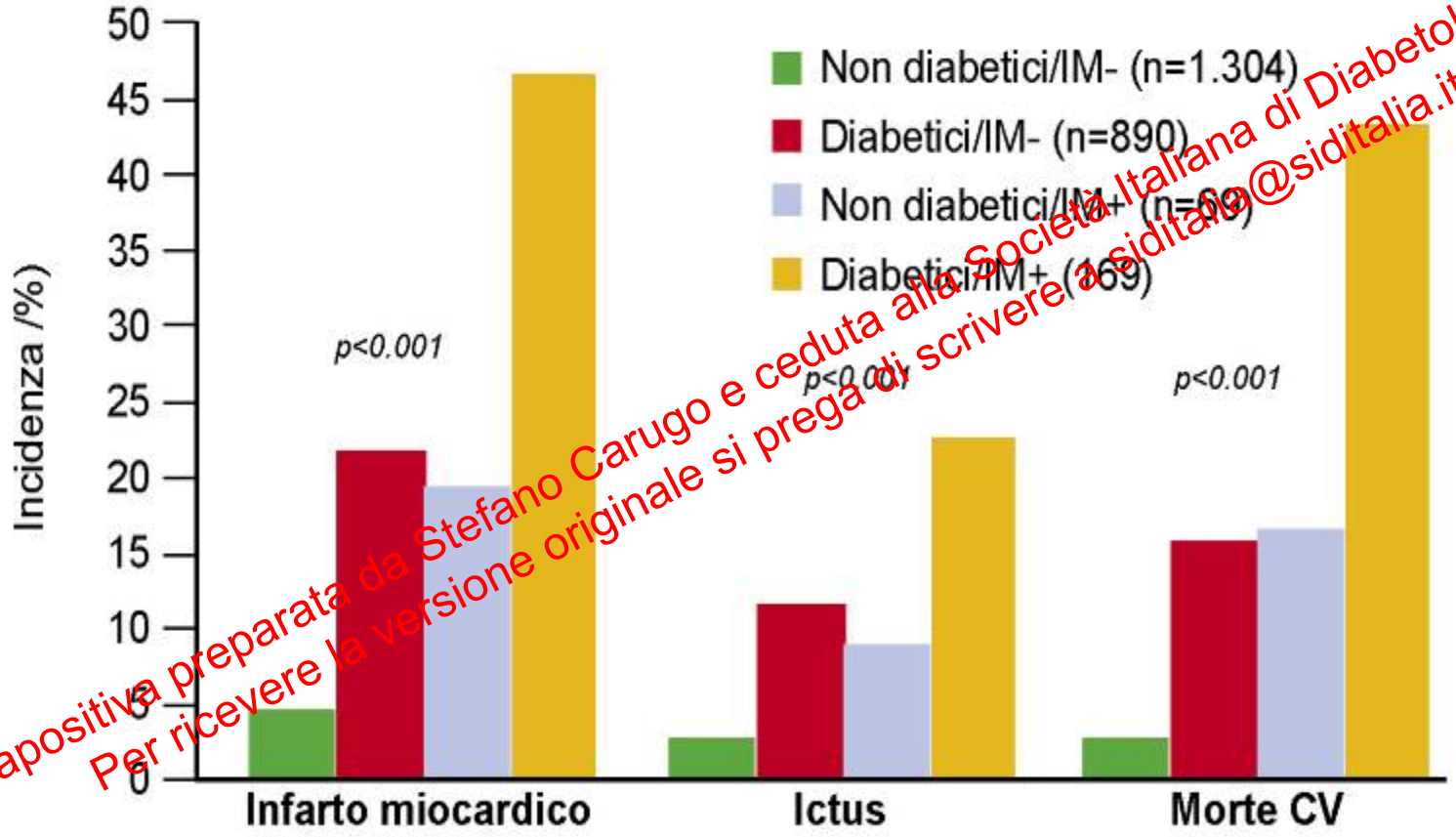
United Kingdom Prospective Diabetes Study (UKPDS:23)

Rischio relativo per CHD:

- Colesterolo LDL (terzile sup. vs inferiore): 2.26
- Pressione arteriosa sistolica (" " "): 1.82
- Emoglobina glicata (" " "): 1.52
- Fumo (si vs no) : 1.41

(R.C. Turner et al., BMJ 316: 823-828, 1998)

Elevato rischio di eventi CV nei pazienti con diabete tipo 2

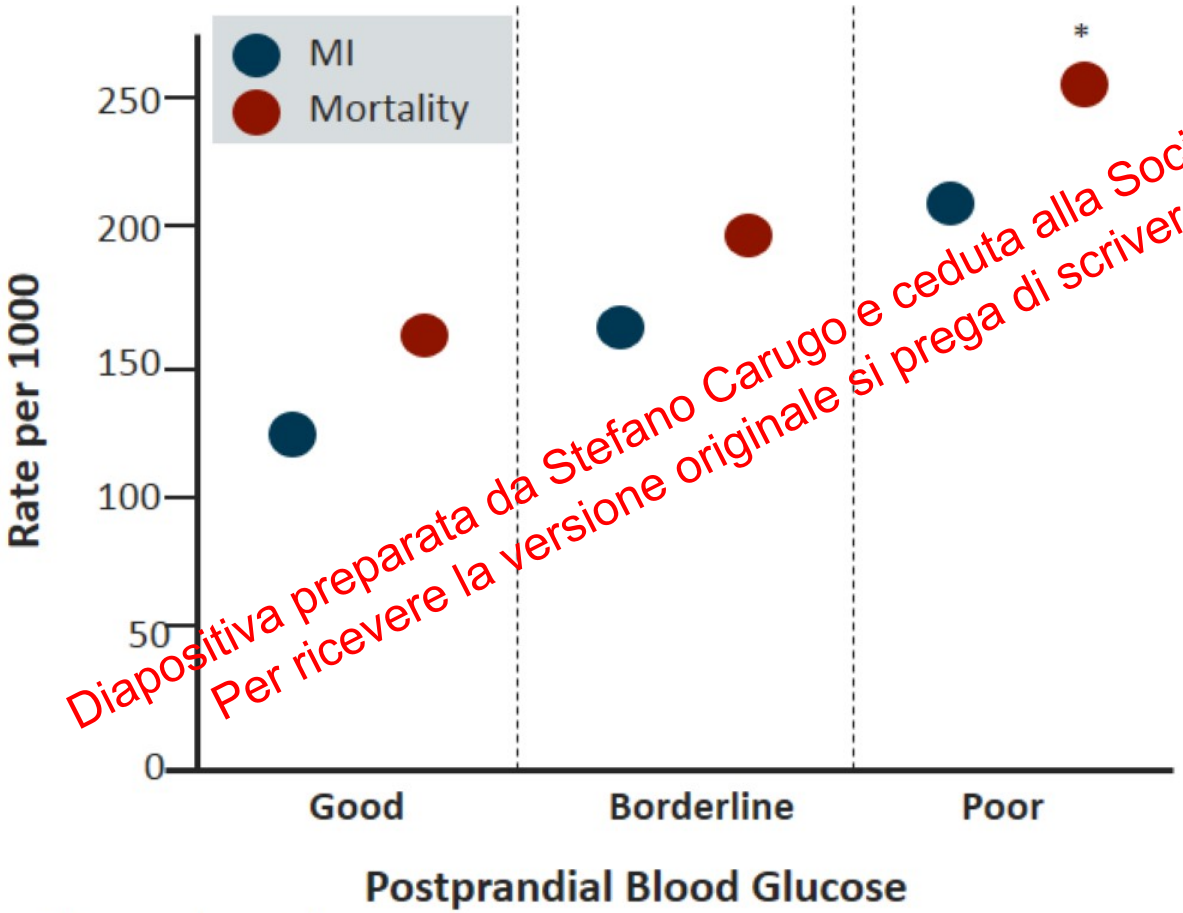


IM-=senza precedente infarto miocardico;
IM+=con precedente infarto miocardico;
CV=cardiovascolari

Haffner SM, N Engl J Med 1998; 339:229-234

T2DM as a Risk Factor for CVD

Chronically Elevated Glycemia, the Key Pathophysiologic Feature of T2DM, Is Itself Associated With Elevated CVD Risk



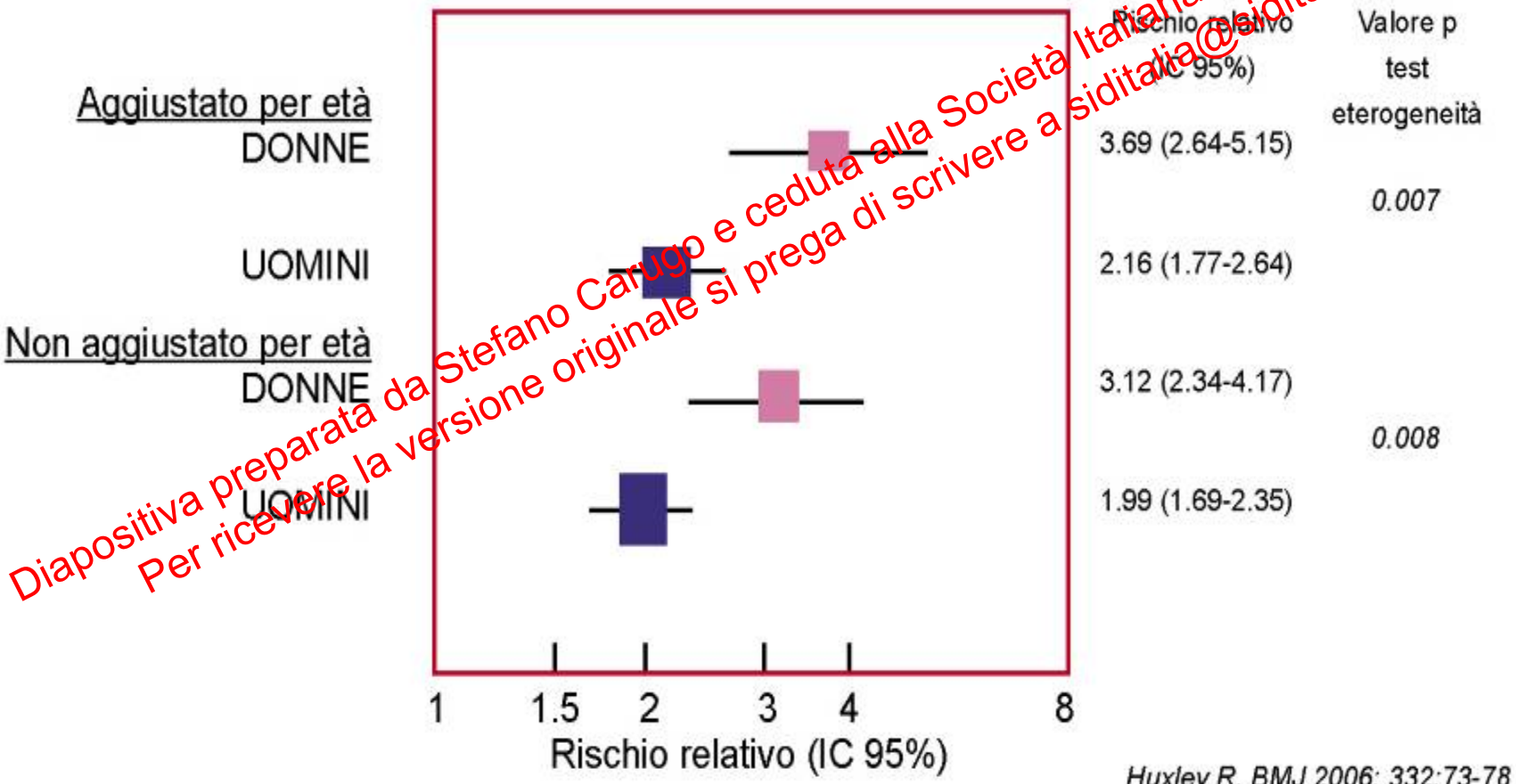
Poor glycemic control was associated with worsening CV outcomes in the long-term follow-up to the Diabetes Prevention Study

*$P < .05$ vs good control

Pistrosch F, et al. *Diabetes Care*. 2011;34(suppl 2):S128-S131.

Eccesso di rischio di malattia coronarica fatale negli uomini e nelle donne con diabete

Meta-analisi di 37 studi prospettici



Huxley R, BMJ 2006; 332:73-78

- **Microvascular complications** of diabetes (retinopathy, nephropathy, and neuropathy) are directly related to the severity and duration of hyperglycaemia, as reflected by the HbA1c.

- **Macrovascular complications** are the primary cause of mortality, with myocardial infarction (MI) and stroke accounting for 80% of all deaths in T2DM patients.

- T2DM patients without prior MI, the 7-year incidence of **MI was double** that of non-diabetic subjects and similar to that of non-diabetic subjects with a prior MI.

- **Recurrence** of major atherosclerotic events in T2DM individuals with a prior MI is very high, 6% per year,30 and death rate in T2DM patients is approximately
two-fold greater than in matched non-diabetic individuals.

End-point cardiovascolari

Soft

- Angina stabile
- Angina induc.
- Ischemia ECG
- ABI ↓

Hard

- Scompenso
- Angina Instab.
- Rivascol.
- Amputazione

«canonici»

- Morte CV
- IMA NF
- Stroke NF

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Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D., Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc., Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

In Sweden from 1998 through 2014, mortality and the incidence of cardiovascular outcomes declined substantially among persons with diabetes, although fatal outcomes declined less among those with type 2 diabetes than among controls.

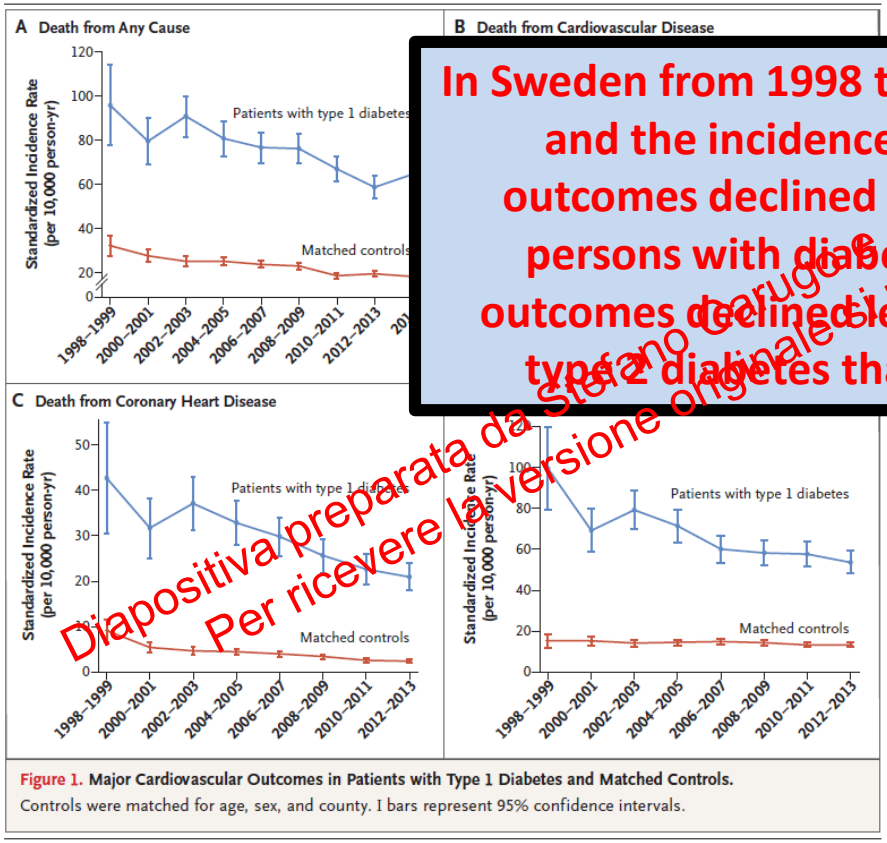


Figure 1. Major Cardiovascular Outcomes in Patients with Type 1 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

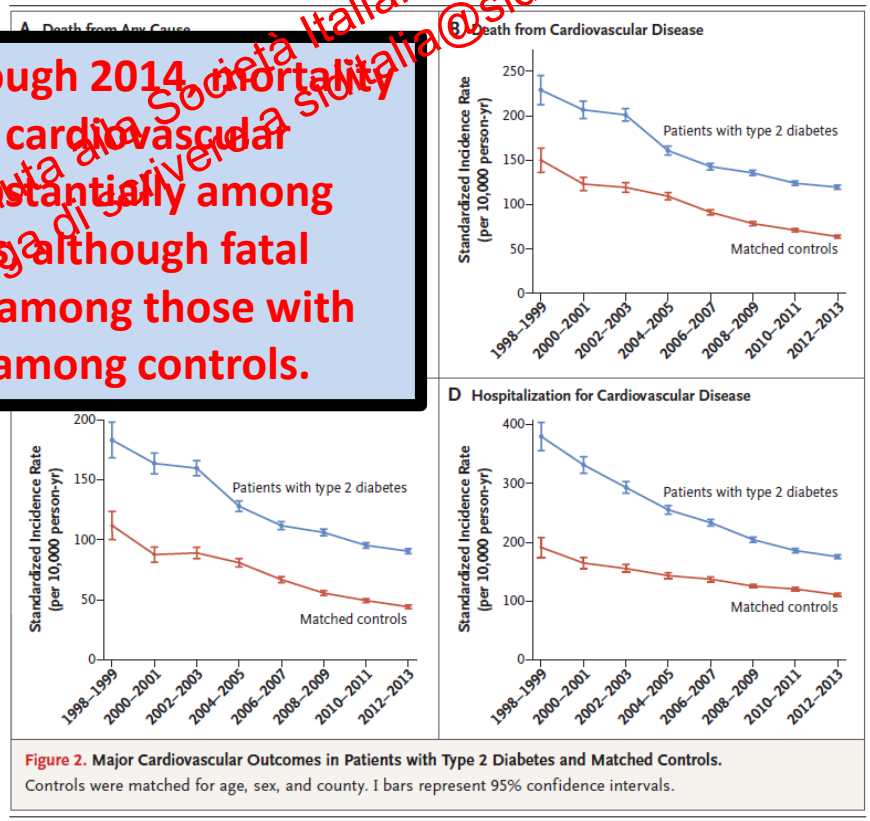
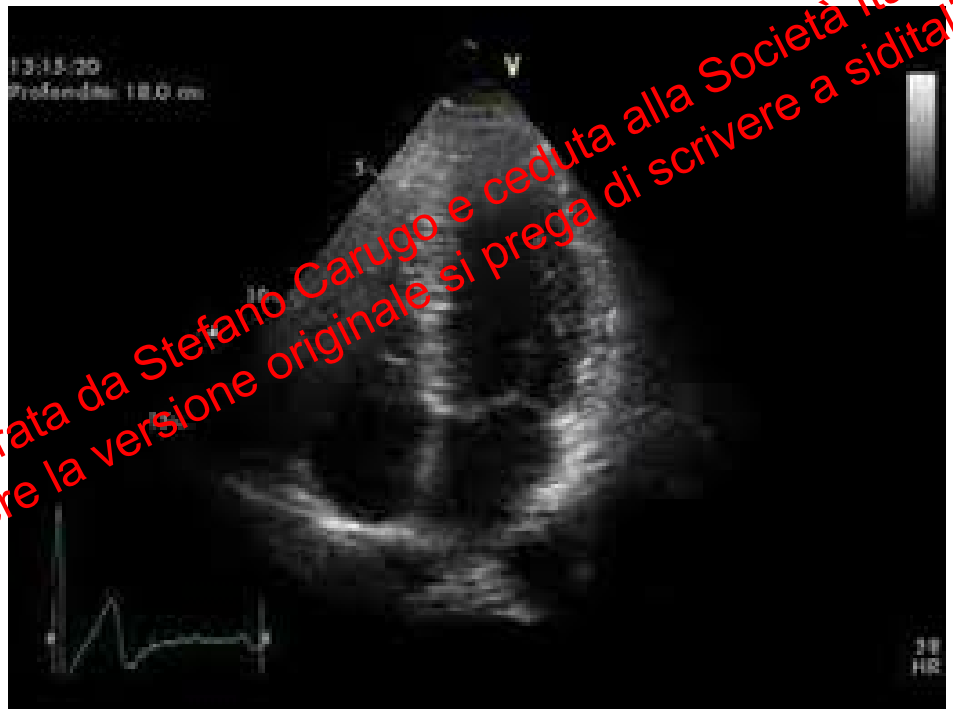


Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.
Controls were matched for age, sex, and county. I bars represent 95% confidence intervals.

A sustained 1% decrement in HbA1c can be expected to reduce coronary risk by 10–15%

Cardiomiopatia Diabetica



Diabetic cardiomyopathy refers to diabetes-associated structural and functional myocardial dysfunction not related to other confounding traditional factors such as coronary artery disease (CAD), hypertension, congenital heart diseases or valvular heart diseases

Diabetic cardiomyopathy

- Diabetic cardiomyopathy is differentiated into two phenotypes:

  1. restrictive or heart failure with preserved left ventricular ejection fraction (HFPEF)

  2. dilated or heart failure with impaired or reduced left ventricular ejection fraction (HFREF).

- The phenotype-specific pathophysiological mechanisms for the DCM phenotypes proposed for left ventricular (LV) remodeling and dysfunction consist of:

- coronary microvascular endothelial dysfunction for HFPEF

- cardiomyocyte cell death for HFREF

Restrictive/HFPEF or Dilated/HFREF phenotypes

- Diabetes mellitus-induced metabolic derangements such as hyperglycemia, lipotoxicity, and hyperinsulinemia favor development of DCM with the restrictive/HFREF type, which is more prevalent in obesity

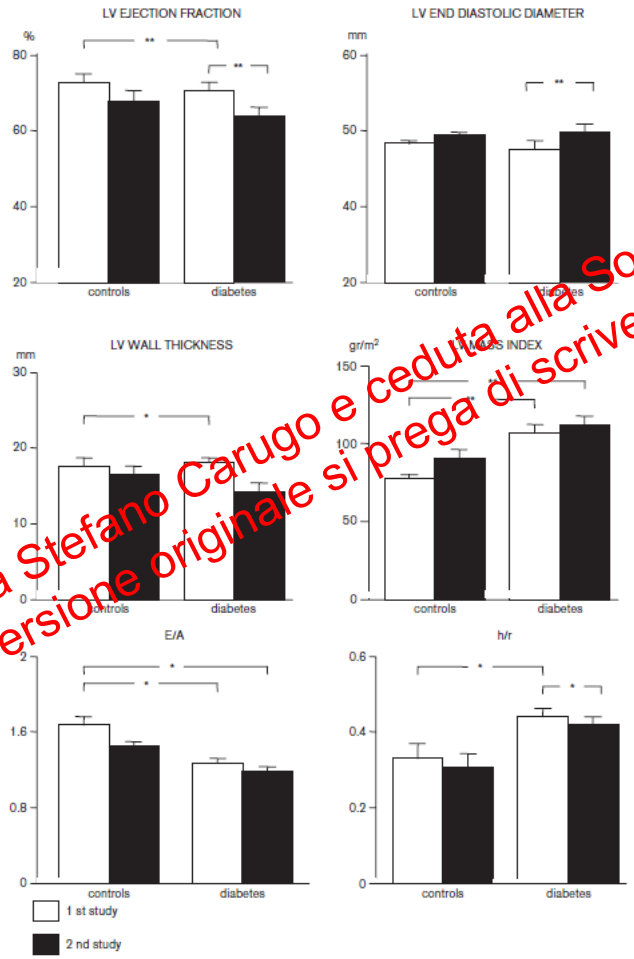
- autoimmunity predisposes to the dilated/HFREF phenotype, which manifests itself more in type 1 DM.

- coronary microvascular rarefaction and advanced glycation end products (AGEs) deposition are relevant pathognomic abnormalities in both phenotypes.

Progression of functional and structural cardiac alterations in young normotensive uncomplicated patients with type 1 diabetes mellitus

Stefano Carugo[a], Cristina Giannattasio[a,b], Ivan Calchera[a], Felice Paleari[a], Maria Grazia Gorgoglione[a], Alessandra Grappiolo[a], Pierluigi Gamba[a], Giovanni Rovaris[a], Monica Failla[a] and Giuseppe Mancia[a,b]

Fig. 1



Echocardiographic data in 56 patients and 20 controls at first study and 2 years later (second study). Data are shown as means ± SE. LV, left ventricular; E/A, ratio between early and late ventricular filling; h/r, ratio between LV wall thickness and diameter. * $P < 0.01$; ** $P < 0.05$.

Journal of Hypertension 2001, 19:1675±1680

Mechanisms

- **Protein kinase cyclase activation**
- **Lipotoxicity**
- **Oxidative stress**
- **Myocardial or interstitial fibrosis**
- **Mitochondrial dysfunction**

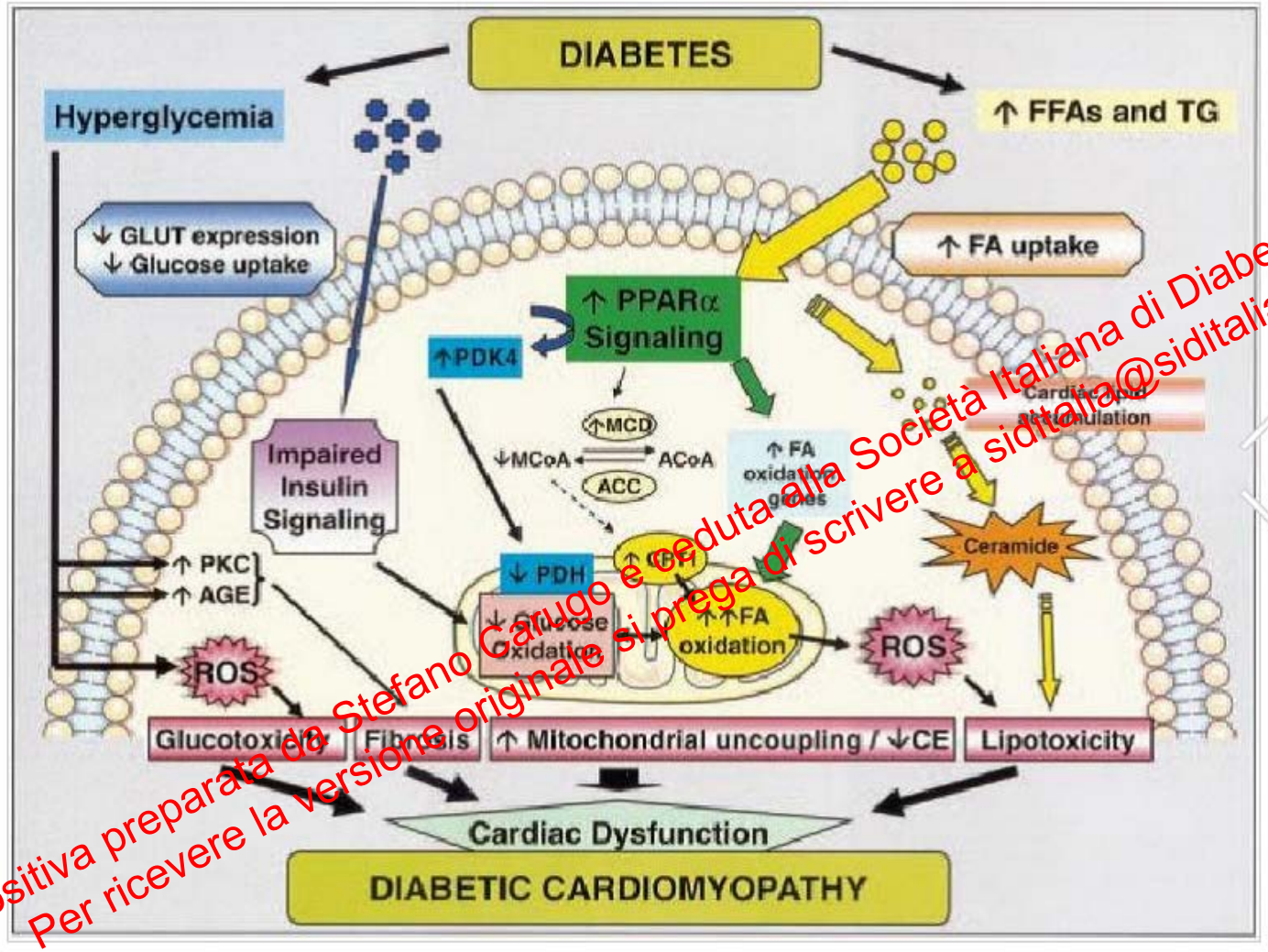


Figure 1. Pathways leading to the development of diabetic cardiomyopathy. ACC: acetyl coenzyme A carboxylase; ACoA: acetyl coenzyme A; AGEs: advanced glycation end products; CE: cardiac efficiency; FA: fatty acids; FFA: free fatty acids; GLUTs: glucose transporters; MCD: malonyl coenzyme A; PDH: pyruvate dehydrogenase; PDK: pyruvate dehydrogenase kinase; PKC: protein kinase C; PPARα: peroxisome proliferator-activated receptor alpha; TG: triglycerides [2, 5]

Protein kinase cyclase activation

- Hyperglycemia exerts its deleterious myocardial and cardiovascular effects through protein kinase C/diacylglycerol (PKC/DAG) signaling pathway, leading to cardiac fibrosis through **activation of the connective tissue growth factor**

- The activation of PKC/DAG pathways induces multiple changes in DCM which include **reduction in tissue blood flow**, enhanced extracellular matrix deposition, capillary basement membrane thickening and increased vascular permeability with alterations in neovascularization

Lipotoxicity

- Diabetic cardiomyopathy is characterized by significant deposition of **lipofuscin**.
- **Increased myocardial triglyceride (TG) and cholesterol** content have also been reported in the myocardial samples of DM patients independent of circulating levels of TG in DM, and also in obesity, insulin resistance and impaired glucose tolerance.
- Type 2 DM which is most often associated with obesity leads to myocardial lipotoxicity that may in turn lead to **cell death** and subsequently cardiac dysfunction, particularly diastolic.
- The changes in the composition of **endoplasmic reticulum (ER)** membrane phospholipids have also been reported in lipotoxicity, which precipitate ER swelling and ER stress long-chain fatty acids, all interfere with the dynamics of plasma and mitochondrial membranes by altering phospholipid composition
- The saturated long-chain fatty acid, **palmitate**, is another substance which induces apoptosis in cardiomyocytes by diminishing the mitochondrial anionic phospholipid, cardiolipin.

Oxidative stress

- Oxidative stress plays a critical role in the pathogenesis of DCM, as increased oxidative stress is associated with lipid overload.
- Lipids, particularly **free fatty acids**, are important in generating reactive oxygen species (ROS), which are deleterious in DM patients
- Diabetic hearts are characterized by **increased cardiac lipid accumulation and mitochondrial free fatty acid oxid**ation, which play an important role in the mechanism of DCM.

The end products of NO and increased ROS contribute to the switch in cardiac myosin heavy chain which could be detrimental in patients with long-standing DM

Myocardial or interstitial fibrosis

- **Interstitial and perivascular fibrosis** are pathological hallmarks of DCM . In addition, studies have reported collagen deposition around intramural vessels and also between the myofibers in diabetic heart

- Diastolic dysfunction in diabetes has been correlated with **pro-collagen type I** carboxy-terminal peptide. This plays a crucial role in the pathological mechanism of myocardial fibrosis in diabetic patients with documented LV myocardial dysfunction

- Extracellular fibrosis and collagen deposition which resembles LV myocardium of a human with type 2 diabetes, with **an increase in transforming growth factor** (**TGFβ1**) receptor II density in the myocardium has been reported in animal studies

- TGFβ is one of several cytokines in gene expression enhanced by diabetes

Mitochondrial dysfunction

Il rischio residuo

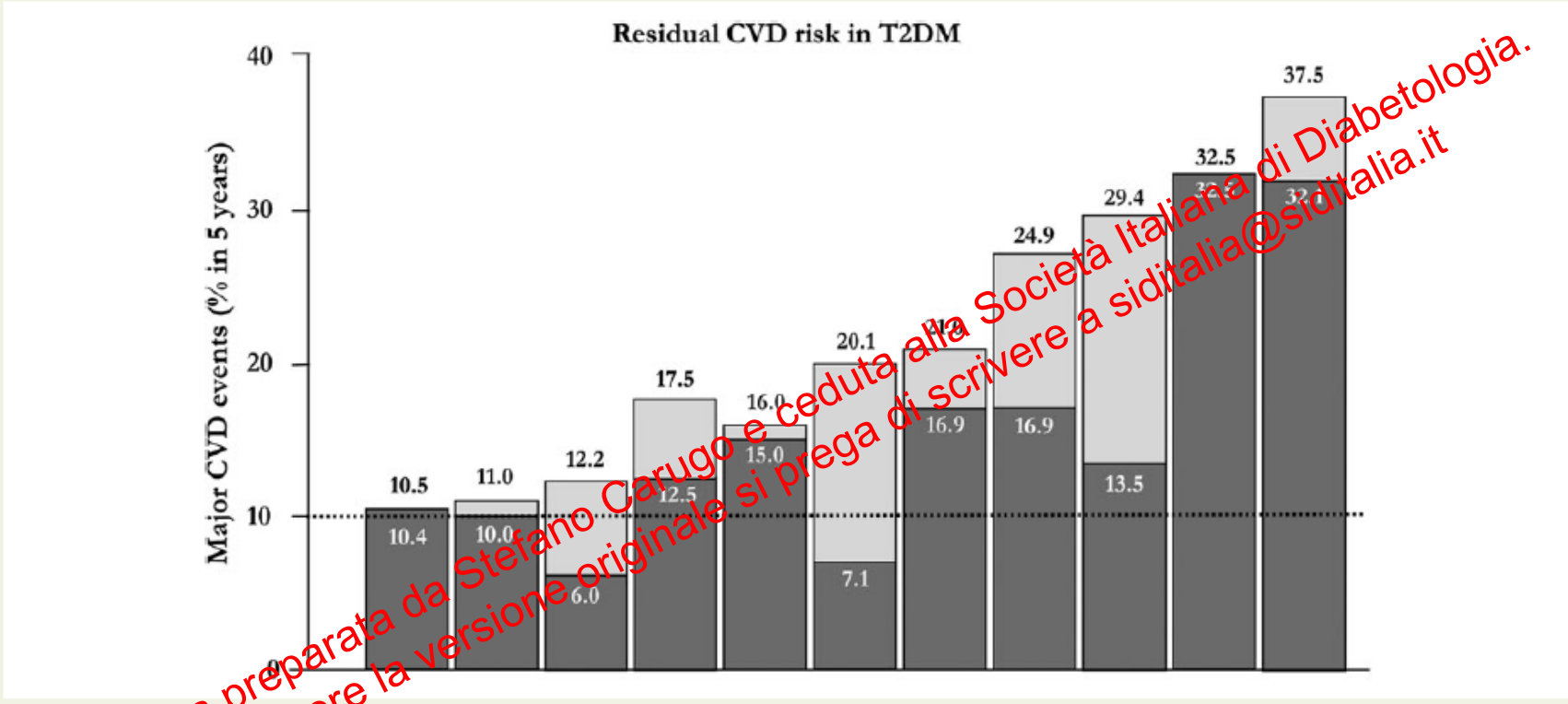


Figure 3 Five-year risk of major cardiovascular events in the diabetic cohorts of randomized trials of anti-hypertensive treatment. The height of each bar is the baseline risk in rank order from lowest to highest, the light grey areas are the median treatment-induced risk reduction. The dark grey bars show that the residual cardiovascular disease risk is generally higher than the baseline risk. Redrawn from Ref.[324].

In high-risk patients CVD risk reduction is indeed greater than in low-risk subjects but their residual risk remains high (and higher than in low-risk subjects). In other words, residual risk appears to be roughly proportional to baseline risk

DOBBIAMO QUINDI ESSERE PIU' AGGRESSIVI?

Three recent prospective trials—**ADVANCE, ACCORD, and VADT3**—in high-risk T2DM patients tested the ability of intensified glycaemic control to protect against CVD. Baseline HbA1c was 7.2% in ADVANCE, 8.1% in ACCORD, and 9.4% in VADT.

After intensive therapy, HbA1c dropped to 6.4% in ACCORD and ADVANCE and to 6.9% VADT; after standard therapy, the values were 7.5, 7.0, and 8.4%, respectively.

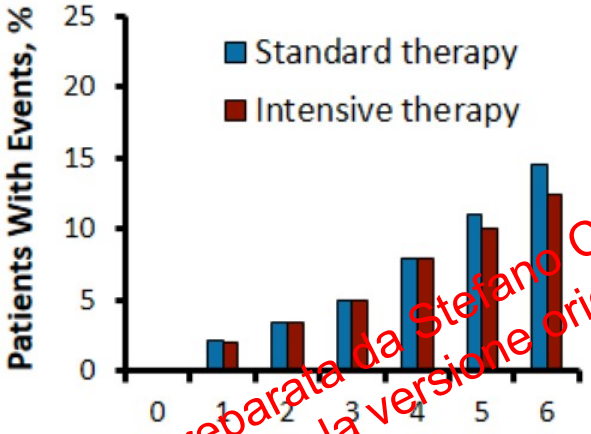
None of these studies showed a decrease in incident CVD

Despite a significant reduction in ischaemic cardiac events (MI, revascularization, and unstable angina) in the intensive treatment group, **ACCORD** was stopped prematurely because of increased mortality.

Intensive Glycemic Control Increased All-Cause Mortality (ACCORD)

Primary Outcome[a]

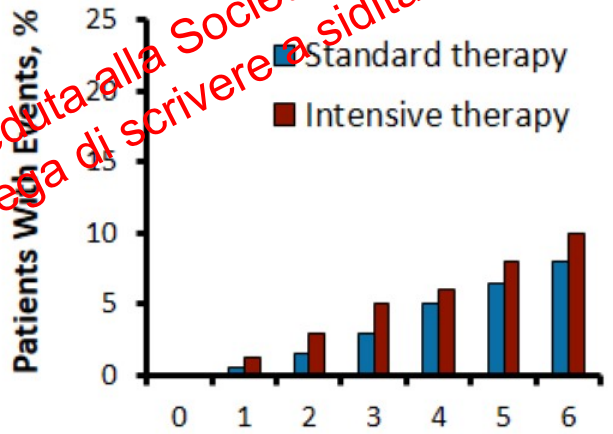
Nonsignificant reduction in CV events in intensive group (HR = 0.90, *P* = .16)



No at risk							
Intensive therapy	5128	4841	4390	2839	1337	475	448
Standard therapy	5123	4827	4262	2702	1186	440	395

Death From Any Cause[a]

Increased mortality in intensive group (HR = 1.22, *P* = .04)



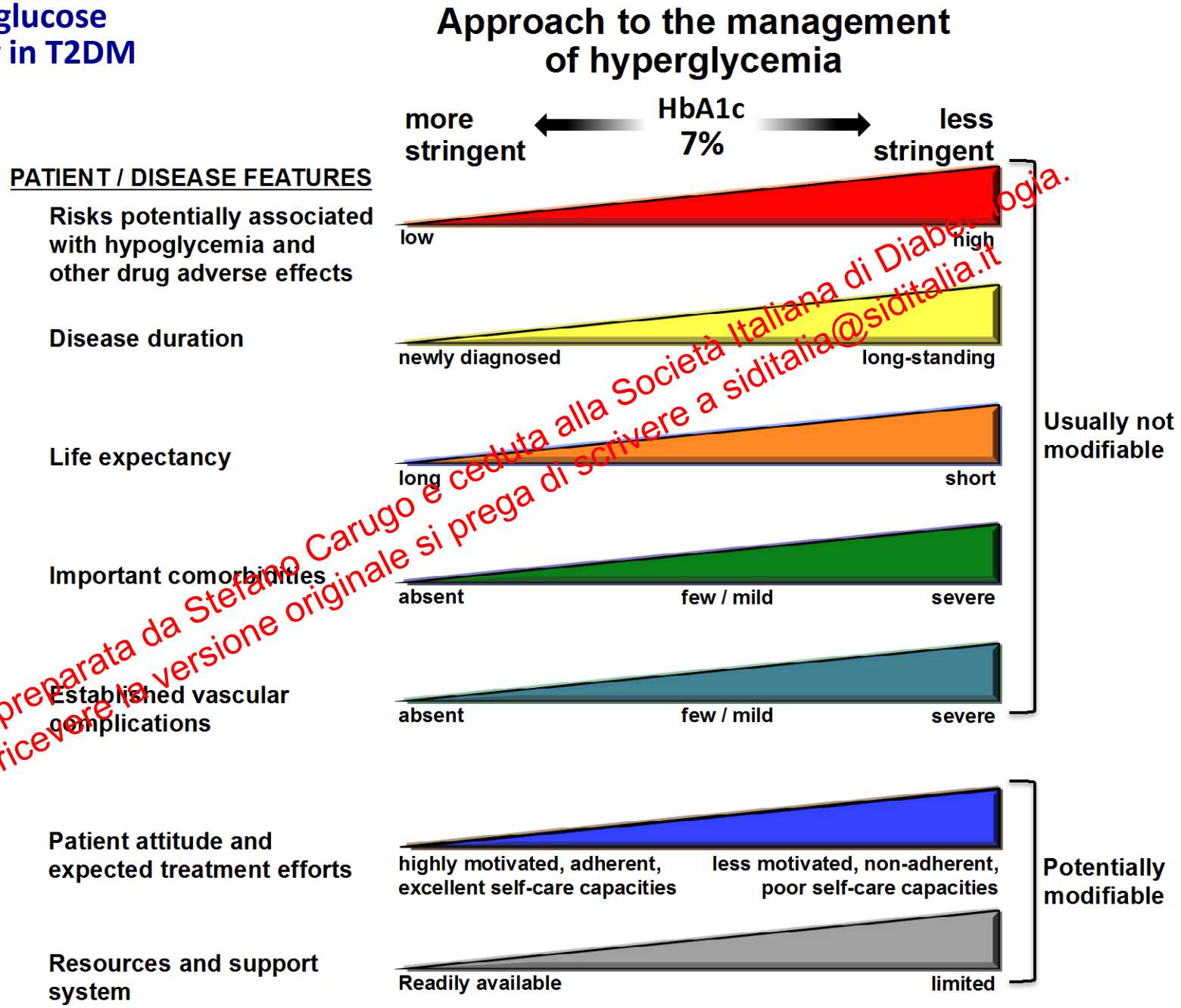
	5128	4972	4803	3250	1748	523	506
	5123	4971	4700	3180	1642	499	480

Mortality did not increase in other outcome trials (eg, VADT and ADVANCE)[b,c]

*MACE: nonfatal MI, nonfatal stroke, or CV death

a. ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559.
b. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139.
c. ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM



Diabetes Care 2015;38:140-149; *Diabetologia* 2015;58:429-442

Il trattamento

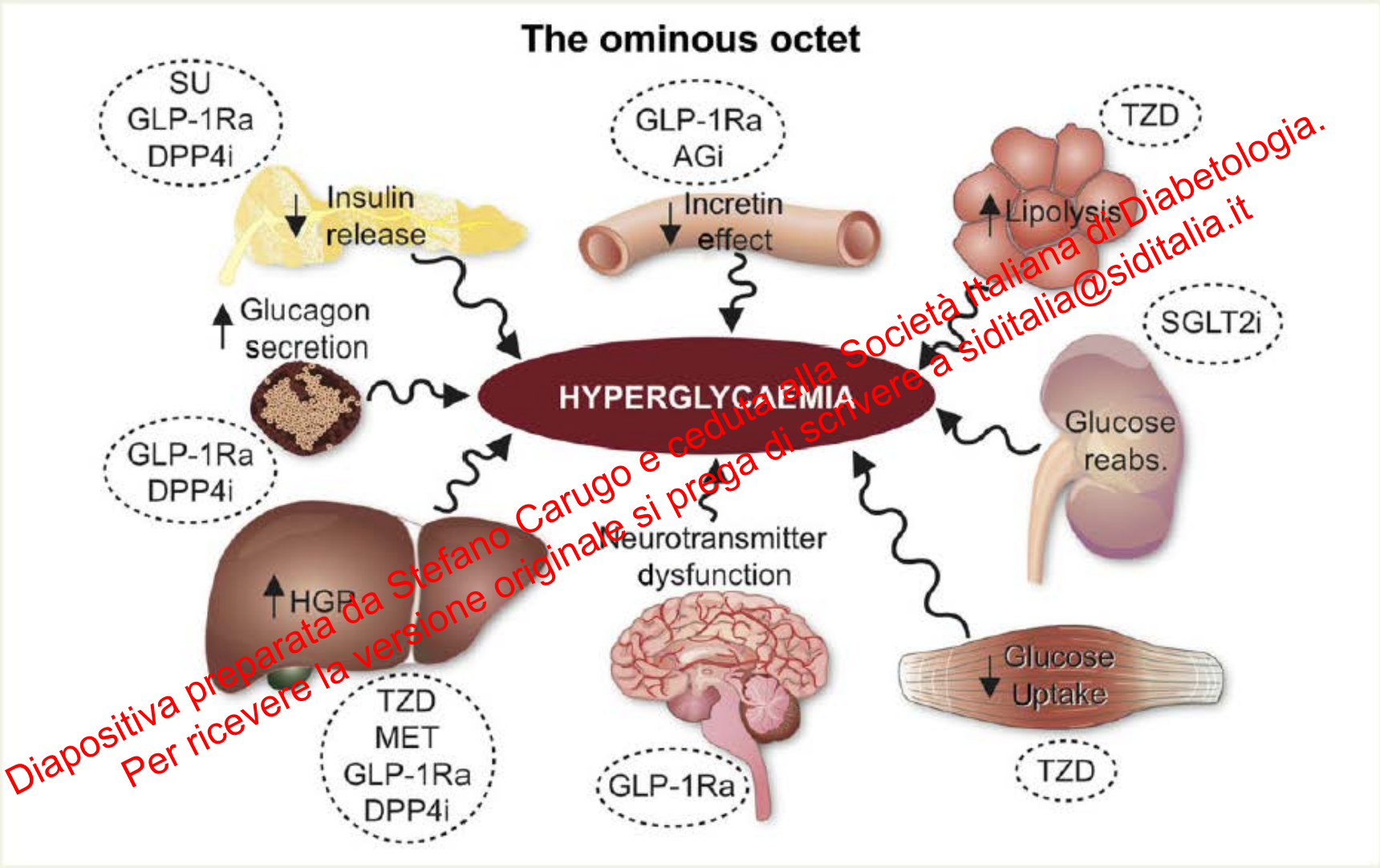


Figure 1 Mechanistic contribution of different tissues to hyperglycaemia. The arrows indicate the direction of change in function; site and mode of action of glucose-lowering drugs are shown in the dotted circles. HGP, hepatic glucose production; GLP-1Ra, GLP-1 receptor agonists; TZDs, thiazolidinediones; DPP4i, DPP4 inhibitors; SGLT2i, SGLT2 inhibitors; SU, sulfonylureas; AGi, α-glucosidase inhibitors.

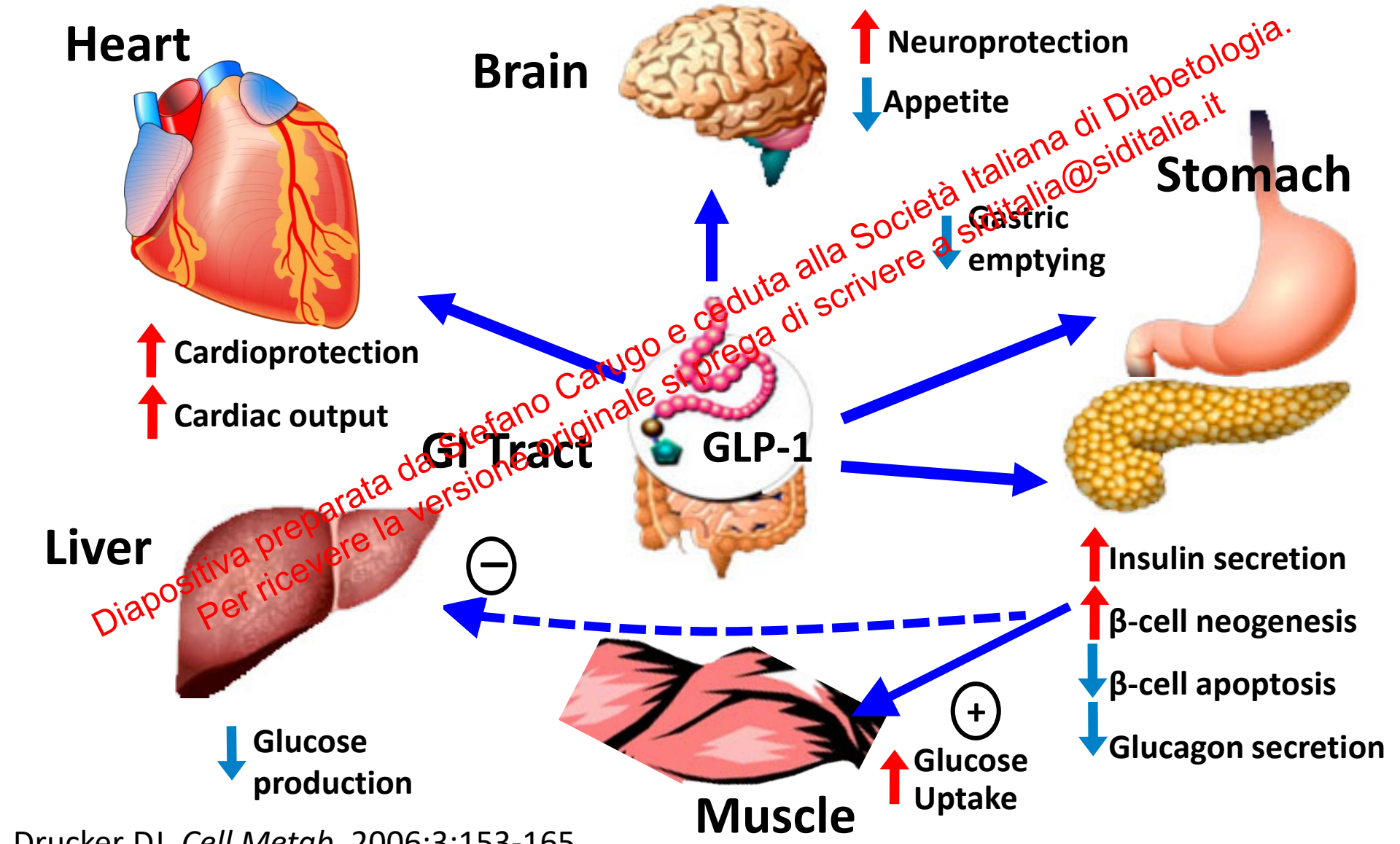
l **GLP-1** hanno la funzione di controllare la glicemia in vari modi:

1.aumentando la secrezione di insulina da parte delle cellule beta del pancreas

2. diminuendo la secrezione di glucagone (antagonista dell'insulina) da parte delle cellule alfa del pancreas

3.rallentando la motilità e dunque lo svuotamento gastrico (rendendo più "soft" la curva glicemica postprandiale) e diminuendo l'appetito.

GLP-1 Actions in Peripheral Tissue



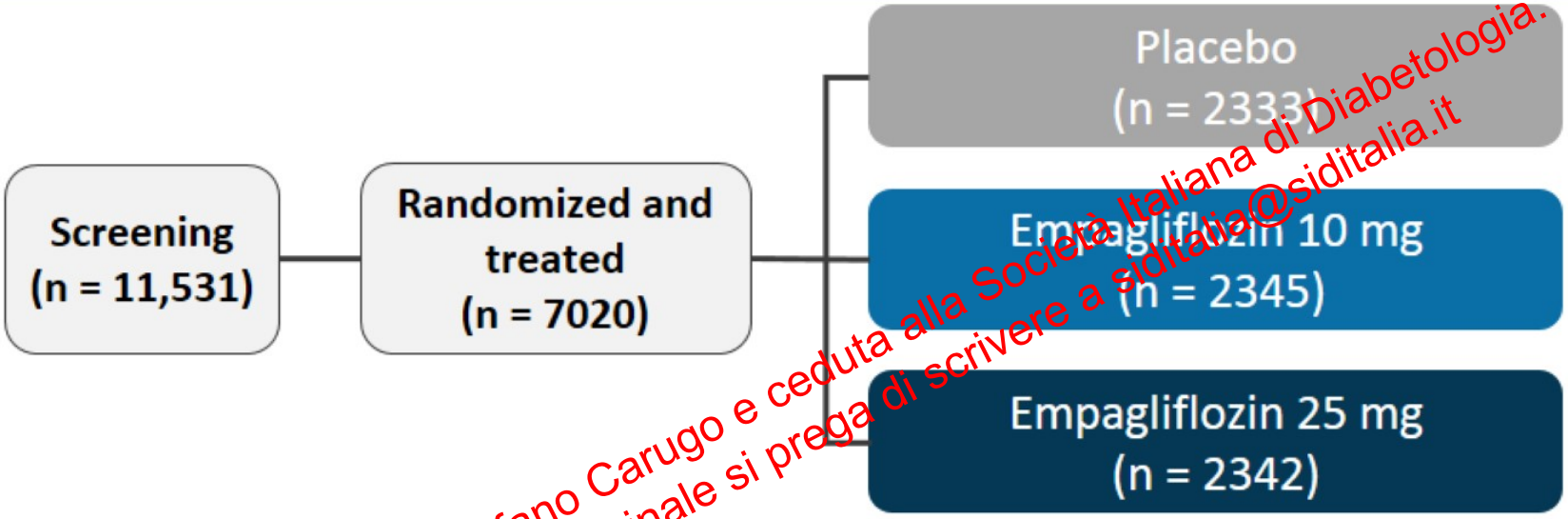
Drucker DJ. *Cell Metab*. 2006;3:153-165.

Injectable Class	Mechanism	Advantages	Disadvantages	Cost
Amylin mimetics	• Activates amylin receptor • ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • ↓ Postprandial glucose	• Gastrointestinal • Modest ↓ A1c • Injectable • Hypo if insulin dose not reduced • Dosing frequency • Training requirements	High
GLP-1 receptor agonists	• Activates GLP-1 R • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• ↓ Weight • No hypoglycemia • ↓ Postprandial glucose • ↓ Some CV risk factors	• Gastrointestinal • ? Pancreatitis • ↑ Heart rate • Medullary ca (rodents) • Injectable • Training requirements	High
Insulin	• Activates insulin receptor • Myriad	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Patient reluctance • Training requirements	Variable

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442

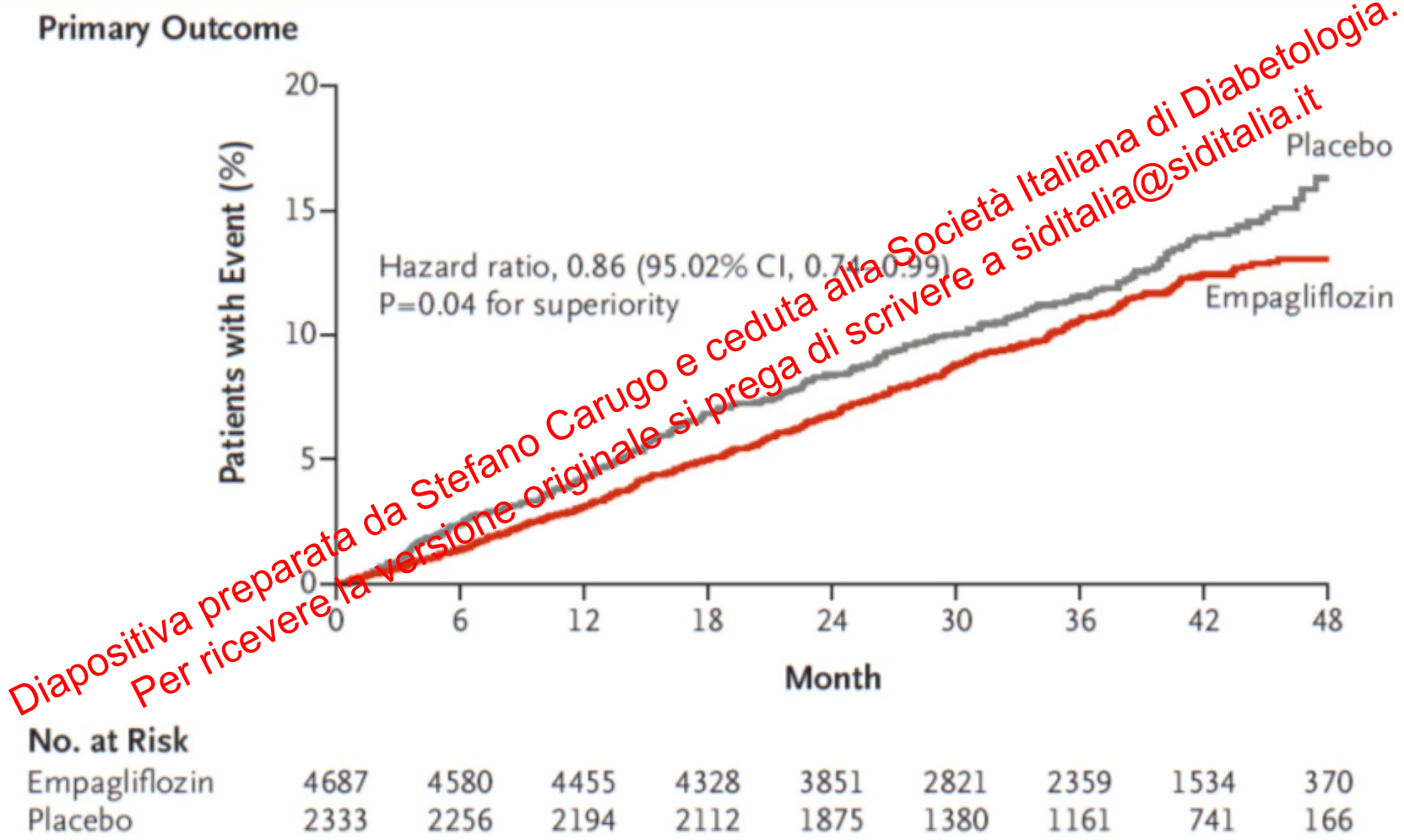
EMPA-REG OUTCOME: Trial Design



- 7020 patients randomly assigned to placebo, empagliflozin 10 mg once daily, or empagliflozin 25 mg once daily
- Study medication was given in addition to standard of care
- The trial was to continue until ≥ 691 patients experienced an adjudicated primary outcome event
- Key inclusion criteria:
  - Adults with T2DM and established CVD
  - BMI ≤ 45 kg/m^2; HbA1c 7% to 9% (drug-naive subgroup); HbA1c 7% to 10% (nondrug-naive subgroup); eGFR ≥ 30 mL/min/1.73m^2; MDRD

Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128.

EMPA-REG Primary Outcome (3-Point MACE): CV Death, Nonfatal MI, or Nonfatal Stroke



Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128. Copyright © 2015 Massachusetts Medical Society.
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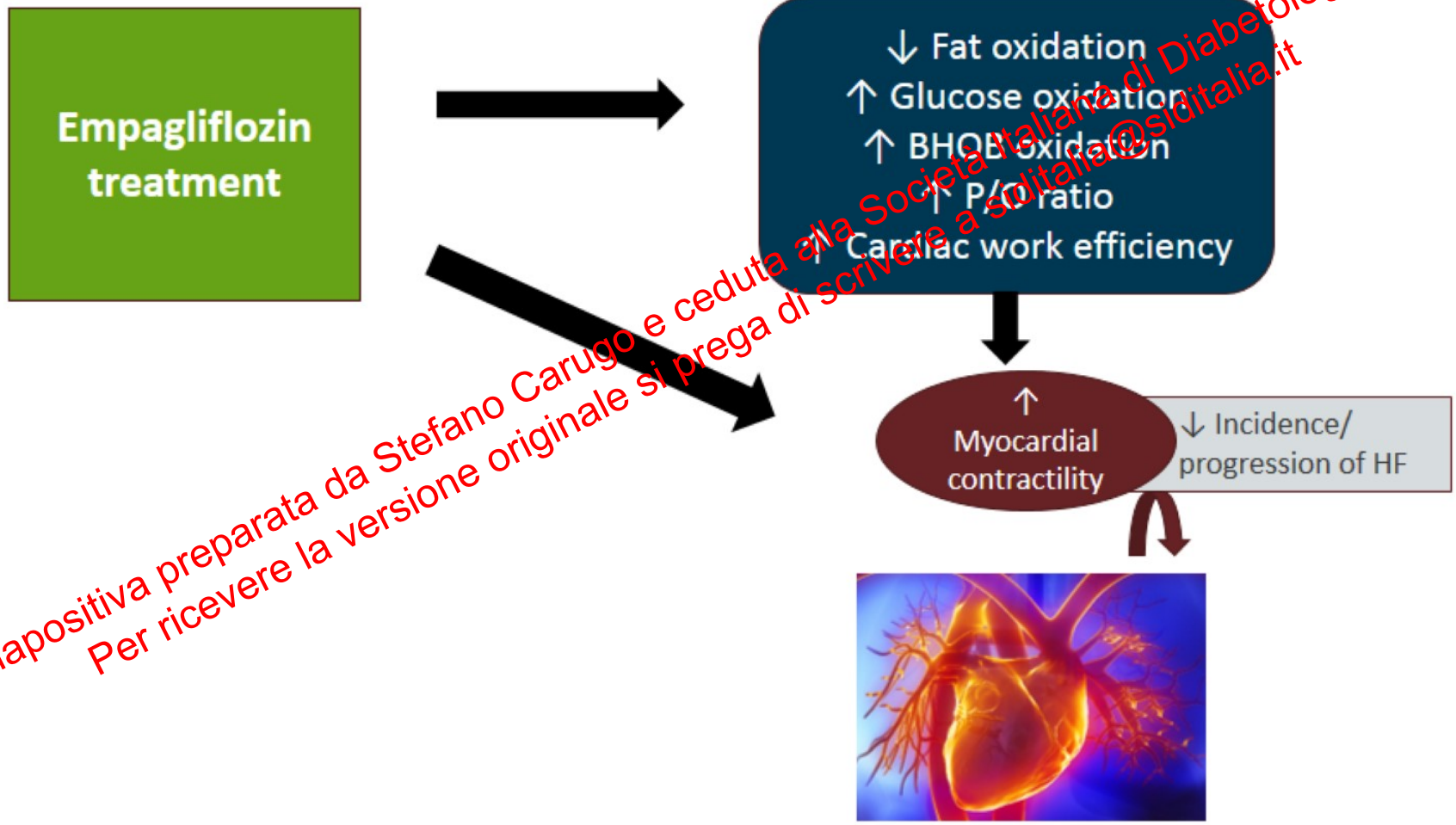
The "Fuel Hypothesis" as Explanation of Empagliflozin's Cardiorenal Benefits



Mudaliar S, et al. *Diabetes Care*. 2016;39:1115-1122.

SGLT2 Inhibitors and Reduced Volume Overload

- SGLT2 inhibitors decrease proximal tubular sodium and chloride reabsorption, leading to a reset of the tubuloglomerular feedback
- This induces plasma volume contraction without activation of the sympathetic nervous system, decreases harmful glomerular hyperfiltration leading to better long-term renal preservation, and improves diuretic and natriuretic responses to other diuretic agents

Martens P, et al. *Curr Treat Options Cardiovasc Med*. 2017;19:23.

Oral Class	Mechanism	Advantages	Disadvantages	Cost
α-Glucosidase inhibitors	• Inhibits α-glucosidase • Slows carbohydrate digestion / absorption	• No hypoglycemia • Nonsystemic • ↓ Postprandial glucose • ? ↓ CVD events	• Gastrointestinal • Dosing frequency • Modest ↓ A1c	Mod.
DPP-4 inhibitors	• Inhibits DPP-4 • Increases incretin (GLP-1, GIP) levels	• No hypoglycemia • Well tolerated	• Angioedema / urticaria • ? Pancreatitis • ? ↑ Heart failure	High
Bile acid sequestrants	• Bind bile acids • ? ↓ Hepatic glucose production	• No hypoglycemia • ↓ LDL-C	• Gastrointestinal • Modest ↓ A1c • Dosing frequency	High
Dopamine-2 agonists	• Activates DA receptor • Alters hypothalamic control of metabolism • ↑ Insulin sensitivity	• No hypoglyemia • **?** ↓ CVD events	• Modest ↓ A1c • Dizziness, fatigue • Nausea • Rhinitis	High
SGLT2 inhibitors	• Inhibits SGLT2 in proximal nephron • Increases glucosuria	•↓ Weight • No hypoglycemia • ↓ BP • Effective at all stages	• GU infections • Polyuria • Volume depletion • ↑ LDL-C • ↑Cr (transient)	High

Table 1. Properties of anti-hyperglycemic agents

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442

CONCLUSIONI

Maggiore collaborazione tra cardiologi e diabetologi

Il paziente al centro

Ospedale San Paolo
Polo Universitario

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

UNIVERSITÀ DEGLI STUDI DI MILANO

Grazie per l'attenzione

Centro Cuore San Paolo